

## Extensive determination of glycan heterogeneity reveals an unusual abundance of high-mannose glycans in enriched plasma membranes of human embryonic stem cells.

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### Public Summary:

Human embryonic stem cells can give rise to virtually any cell type in the adult body, a characteristic termed pluripotency. Because of this unique capability, these cells have the potential to cure a vast majority of existing human disorders. However, the components that make stem cells different than mature cells have not been fully identified. Cells in the human body have an outer coating which consists largely of sugars. These sugars serve as a first point of contact for cells with the environment and with other cells and, therefore, are uniquely poised to participate in communication processes that govern the fate of cell - whether it be to adapt to a stress in the environment, or to respond to growth signals that tell a stem cell to differentiate into a mature cell type such as those in muscle, nerve or bone. Our research presented herein provides fundamental characterization of the sugars which coat the cell membranes of pluripotent stem cells. We found that stem cells abundantly possess a sugar called high-mannose that is very unusual to observe on the membranes of human cells. Future work will seek to understand why this high mannose is produced by stem cells and displayed on their surfaces, and what possible functions high mannose may have in contributing to the survival of stem cells and in the maintenance of pluripotency properties.

### Scientific Abstract:

Most cell membrane proteins are known or predicted to be glycosylated in eukaryotic organisms, where surface glycans are essential in many biological processes including cell development and differentiation. Nonetheless, the glycosylation on cell membranes remains not well characterized due to the lack of sensitive analytical methods. This study introduces a technique for the rapid profiling and quantitation of N- and O-glycans on cell membranes using membrane enrichment and nanoflow liquid chromatography/mass spectrometry of native structures. Using this new method, the glycome analysis of cell membranes isolated from human embryonic stem cells and somatic cell lines was performed. Human embryonic stem cells (hESCs) were found to have high levels of high-mannose glycans, which contrasts with IMR-90 fibroblasts and a human normal breast cell line, where complex glycans are by far the most abundant and high-mannose glycans are minor components. O-glycosylation is relatively minor components of cell surfaces. To verify the quantitation and localization of glycans on the hESCs membranes, flow cytometry and immunocytochemistry were performed. Proteomics analyses were also performed and confirmed enrichment of plasma membrane proteins with some contamination from endoplasmic reticulum and other membranes. These findings suggest that high-mannose glycans are the major component of cell surface glycosylation with even terminal glucoses. High mannose glycans are not commonly presented on the surfaces of mammalian cells or in serum, yet may play important roles in stem cell biology. The results also mean that distinguishing stem cells from other mammalian cells may be facilitated by the major difference in the glycosylation of the cell membrane. The deep structural analysis enabled by this new method will enable future mechanistic studies on the biological significance of high-mannose glycans on stem cell membranes and provide a general tool to examine cell surface glycosylation.

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